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REVIEW ARTICLE

# Non-convulsive seizures and non-convulsive status epilepticus in neuro-intensive care unit

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Most seizures in critical ill patients are non-convulsive, and some patients may develop non-convulsive status epilepticus (NCSE), a state of continuous or repetitive seizures without convulsions. With the growing use of continuous electroencephalogram (EEG) monitoring in neuro-intensive care units, non-convulsive seizure (NCS) and NCSE are increasingly diagnosed in patients with impaired consciousness, and progress has been made in identifying various EEG characteristics of NCS/NCSE. Epidemiological studies have contributed to a better understanding of etiologies and risk factors for NCS and NCSE. However, sufficient clinical trials about the treatment of NCS and NCSE are still lacking. The appropriate level of aggressiveness in the treatment of NCSE is still debated, particularly with regard to the use of anesthetics in patients with refractory NCSE. In this review, we summarize the EEG, clinical, epidemiological, diagnostic and therapeutic knowledge of NCS and NCSE in the neuro-intensive care setting in detail.

**KEYWORDS**
neuro-intensive care, non-convulsive seizure, non-convulsive status epilepticus

## 1 | INTRODUCTION

Patients in the neuro-intensive care unit (neuro-ICU) are often at high risk for non-convulsive seizure (NCS) and even non-convulsive status epilepticus (NCSE).[1,2] However, due to the diversity and subtlety of symptoms, the prompt and accurate diagnosis of NCS/NCSE is often challenging. Prolonged NCSs and NCSE are often associated with a poor neurological prognosis; therefore, early recognition and rapid treatments are required.[1,3,4] Over the past decade, the use of continuous electroencephalogram (cEEG) has driven the identification of NCS and NSCE, and stepwise approaches to treat NCS and NCSE have been proposed. In this review, we summarize the current knowledge of NCS and NCSE in the neuro-intensive care setting and outline areas for further research.

## 2 | DEFINITION

NCS is a highly heterogeneous clinical condition and broadly defined as a paroxysmal change in behavior and/or mental processes from baseline without convulsive activity, associated with continuous paroxysmal activity or electrographic discharges on the electroencephalogram (EEG).[5,6] NCSE was once defined as a continuous NCS lasting >30 min or multiple NCSs during a period of greater than 30 min and between which sensory, motor, and/or cognitive function was not fully recovered.[7,8] Recently, given the severe neuronal injury and sequelae from prolonged seizures, it has been proposed to shorten the time threshold for NCSE from 30 to 10 min,[9,10] which also provides clinical feasibility for timely initiation of treatment. In addition, electrographic seizures (ESz) and electrographic status epilepticus (ESE) are also common terms in clinical practice. ESz is

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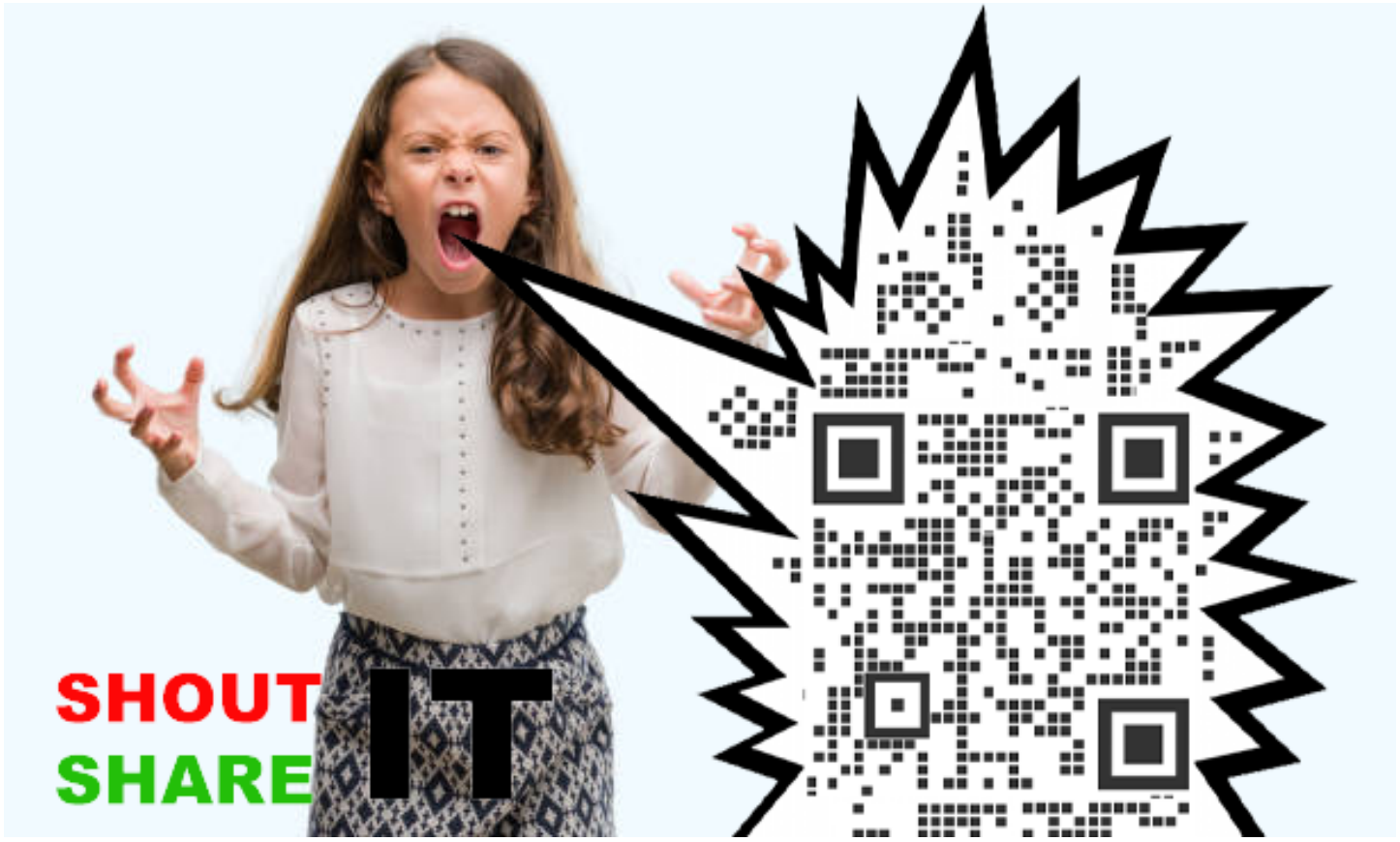
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defined as epileptiform discharges averaging >2.5 Hz for ≧10 s (>25 discharges in 10 s), or any pattern with definite evolution and lasting ≧10 s.[11] ESE is defined as ESz lasting ≧10 continuous minutes or with a total duration of ≧20% of any 60-min period of EEG recording.[11] All the ESz and ESE alone are considered as non-convulsive.[11]

## 3 | EEG CRITERIA

The diagnosis of NCS and NCSE relies mainly on EEG. A unified terminology and classification system for NCSE was proposed in 2013 and is still widely used today. This clinical working criteria for NCSE, known as the Salzburg Consensus Criteria, proposes four EEG Patterns for the diagnosis of NCSE in patients without known epileptic encephalopathy:

1. Epileptiform discharges (spikes, poly spikes, sharp-waves, sharp-and-slow-wave complexes) >2.5 Hz; or,
2. epileptiform discharges ≤2.5 Hz or rhythmic delta/theta activity (>0.5 Hz) AND one of the following:
   a. EEG and clinical improvement after intravenous anti-seizure drugs (ASDs),
   b. subtle clinical ictal phenomena during the EEG patterns mentioned above, or
   c. typical spatiotemporal evolution[12] (Figure 1).

For patients with known epileptic encephalopathy, the diagnosis of NCSE can be made if the EEG shows an increase in the prominence or frequency of the above features compared to baseline with observable change in clinical state, or if an improvement in clinical and EEG features is observed with the use of intravenous ASDs. Several definitions need to be clarified when applying such EEG diagnostic criteria in clinical practice. Typical spatiotemporal evolution is defined as "incrementing onset (voltage increase and frequency change), evolution in pattern (change in frequency >1 Hz or change in location), or decrementing termination (voltage or frequency)".[12] Evolution is defined as "at least 2 unequivocal, sequential changes in frequency, morphology or location". Concretely, evolution in frequency refers to at least two consecutive changes in the same direction by at least 0.5/s; evolution in morphology refers to at least two consecutive changes to a novel morphology; and evolution in location refers to sequentially spreading into or out of at least two different locations of the standard 10–20 electrode.[13] If there is an EEG improvement but no clinical improvement, or if there is fluctuation without definite evolution, possible NCSE should be considered.[12] Fluctuation means "not more than one minute apart, >3 changes in frequency (by at least 0.5/s), >3 changes in morphology, or >3 changes in location (by at least 1 standard interelectrode distance), but not qualifying as evolution".[14] Figure 2 shows examples of EEG

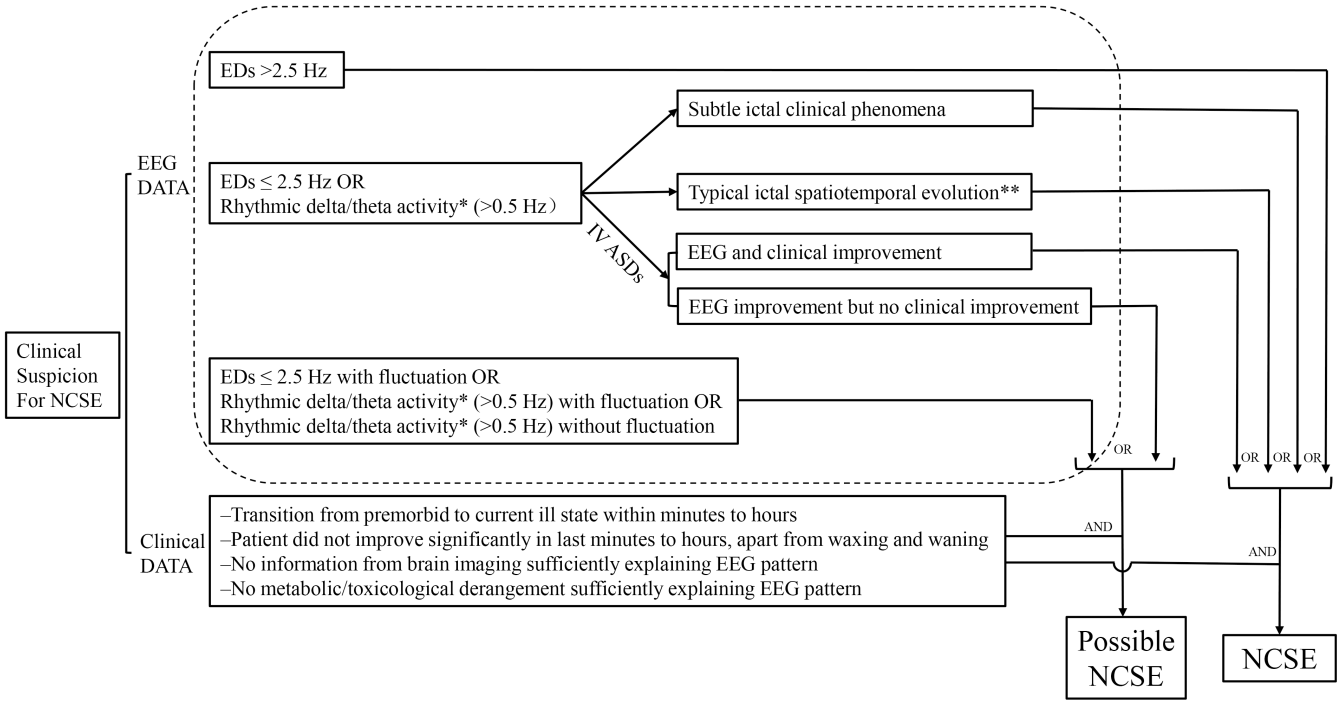
EDs >2.5 Hz
Subtle ictal clinical phenomena
EEG DATA
EDs ≤ 2.5 Hz OR
Rhythmic delta/theta activity* (>0.5 Hz)
Typical ictal spatiotemporal evolution**
IV ASDs
EEG and clinical improvement
EEG improvement but no clinical improvement
Clinical Suspicion For NCSE
EDs ≤ 2.5 Hz with fluctuation OR
Rhythmic delta/theta activity* (>0.5 Hz) with fluctuation OR
Rhythmic delta/theta activity* (>0.5 Hz) without fluctuation
OR
OR OR OR
–Transition from premorbid to current ill state within minutes to hours
–Patient did not improve significantly in last minutes to hours, apart from waxing and waning
–No information from brain imaging sufficiently explaining EEG pattern
–No metabolic/toxicological derangement sufficiently explaining EEG pattern
Clinical DATA
AND
AND
Possible NCSE
NCSE

FIGURE 1 The Salzburg Consensus Criteria for NCSE without known epileptic envephalopathy. American Clinical Neurophysiology Society criterion for rhythmic activity: "Rhythmic = repetition of a waveform with relatively uniform morphology and duration, and without an interval between consecutive waveforms. The duration of one cycle (i.e., the period) of the rhythmic pattern should vary by <50% from the duration of the subsequent cycle for most (>50%) of cycle pairs to qualify as rhythmic".[14] Incrementing onset (increase in voltage and change in frequency), or evolution in pattern (change in frequency >1 Hz or change in location), or decrementing termination (voltage or frequency). NCSE, non-convulsive status epilepticus; EEG, electroencephalogram; EDs: epileptiform discharges (spikes, polyspikes, sharp waves, sharp-and-slow-wave complexes); IV ASDs: intravenous anti-seizure drugs. Information obtained from Beniczk et al. Epilepsia, 2013. 54(Suppl. 6):28–29[12] & M. Leitinger. Epilepsy & Behavior, 2015. 49:158–163[13]

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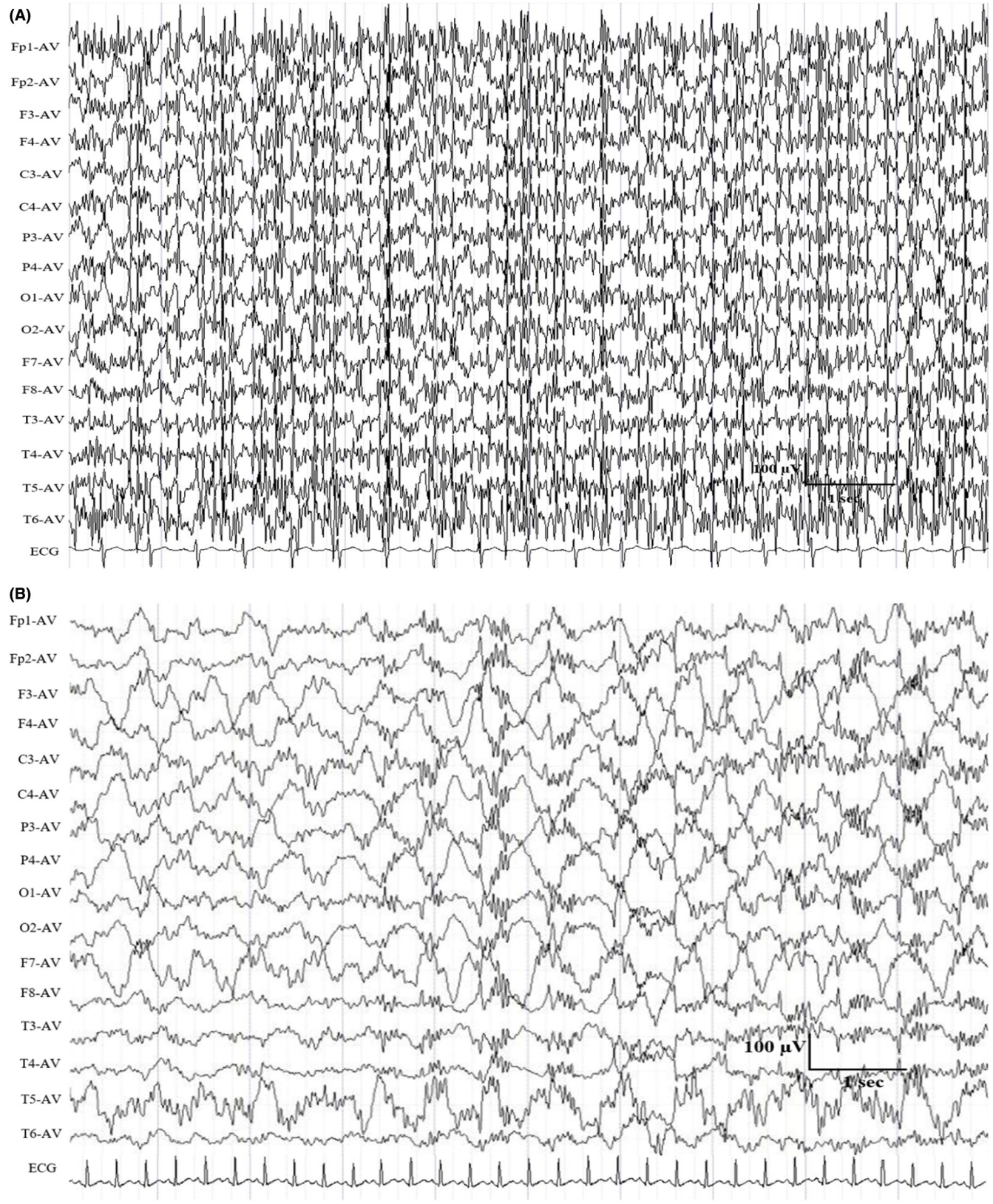


**FIGURE 2** (A) An EEG of a 22 years old woman who was diagnosed with anti-NMDA receptor encephalitis and was admitted to the neuro-ICU due to CSE. The patient was treated with propofol because of the progression to super refractory status epilepticus. Following the CSE, the continuous EEG monitoring demonstrated continuous generalized spike rhythm without clinical manifestations which agreed to the Salzburg Consensus Criteria for NCSE. EEG, electroencephalogram; NMDA, N-methyl d-aspartate; ICU, intensive care unit; CSE, convulsive status epilepticus; NCSE, non-convulsive status epilepticus. (B) An EEG of a 7 years old girl who was diagnosed with antuimmune encephalitis and was admitted to the neuro-ICU in coma. Continuous EEG monitoring demonstrated 1.5–2 Hz rhythmic delta activity with subtle clinical ictal phenomena which was in keeping with Salzburg Consensus Criteria for NCSE. EEG, electroencephalogram; ICU, intensive care unit; NCSE, non-convulsive status epilepticus.

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patterns when applying the Salzburg Consensus Criteria for the diagnosis of NCSE.

Till now, the diagnostic accuracy of Salzburg Consensus Criteria has been validated externally in a number of retrospective studies.[15–19] Most of these studies suggest that the Salzburg Consensus Criteria can be a good tool for the diagnosis of NCSE for less experienced EEG examiners,[16,17] but some details need to be noted. First, perfect concordance between clinical practice and Salzburg Consensus Criteria for NCSE was found for the Definite- and No-NCSE categories.[19] Second, patients with epileptic encephalopathy may receive a false-negative diagnosis when applying Salzburg Consensus Criteria.[16,18] Third, there is no strong data to support the direct and complete inclusion of 'Possible' cases into the true SE category. Some EEG patterns of possible NCSE should be considered as part of the ictal interictal continuum (IIC).[19] IIC is a pattern that does not conform to ESz or ESE, but it may also be contributing to impaired alertness. IIC patterns include: (1) any periodic discharges (PD) or spike-and-wave or sharp-and-wave (SW) pattern that averages >1.0 and ≦2.5 Hz over 10 s; (2) any PD or SW pattern that averages >0.5 and ≦1.0 Hz over 10 s and has a plus modifier or fluctuation; (3) any lateralized RDA averaging >1 Hz for at least 10 s with a plus modifier or fluctuation, including any lateralized rhythmic delta activity (LRDA), bilateral independent rhythmic delta activity, unilateral independent rhythmic delta activity, and multifocal rhythmic delta activity, but not generalized rhythmic delta activity (GRDA).[11] For these patients, it is not clear enough whether treatment should be initiated.[20] Ruijter et al. conducted an open-label trial about the treatment of ESE and found that intensive and stepwise anti-seizure treatment to suppress rhythmic and periodic EEG patterns over a period of at least 48 h did not improve neurologic outcomes at 3 months in comatose survivors after cardiac arrest.[21]

## 4 | SYMPTOMS

NCS/NCSE can present various and subtle symptoms, which include two semiological spectrums: (a) negative symptoms: anorexia, aphasia/mutism amnesia, catatonia, coma, confusion, lethargy and staring; (b) positive symptoms: agitation/aggression, automatisms, blinking, delirium, delusions, echolalia, facial twitching, laughter, nausea/vomiting, nystagmus/eye deviation, perseveration, psychosis and tremulousness.[22] The most common symptoms of NCSE were altered mental status (82%), followed by speech disturbances (15%), myoclonias (13%) and bizarre behavior (11%).[23]

## 5 | CLASSIFICATION

NCS/NCSE can occur in both comatose and non-comatose patients, with the latter also being referred to as the ambulatory or proper forms.[24] The patients with ambulatory or proper forms usually exhibit a wide spectrum of behavioral manifestations, ranging from few or no obvious clinical signs to confusion or mutism. These patients can be classified into three types, namely, generalized NCSE/ absence SE (ASE), focal/localization-related NCSE, and autonomic SE, and usually do not require admission to a neuro-ICU.[24] Conversely, critical ill patients in coma have relatively poor outcomes. Two common types in the neuro-ICU are NCSE in acute brain injury and NCSE following generalized tonic–clonic seizure (GTCS).[24] Table 1 shows the classification of NCSE in detail.

**TABLE 1** Classification of NCSE based on the semiology

| |
|---|
| NCSE with coma (including so-called "subtle" SE) |
| NCSE without coma |
| Generalized |
| 1) Typical absence status |
| 2) Atypical absence status |
| 3) Myoclonic absence status |
| Focal |
| 1) Without impairment of consciousness (aura continua, with autonomic, sensory, visual, olfactory, gustatory, emotional/psychic/experiential, or auditory symptoms) |
| 2) Aphasic status |
| 3) With impaired consciousness |
| Unknown whether focal or generalized |
| 1) Autonomic SE |

*Note*: Adapted from Eugen Trinka. Epilepsia, 2015. 56(10):1515–1523.[9]
Abbreviations: NCSE, non-convulsive status epilepticus; SE, status epilepticus.

## 6 | EPIDEMIOLOGY AND AETIOLOGY

NCS and NCSE can occur in almost any situation that directly or indirectly affects supratentorial homeostasis.[1] NCSE accounts for about 21%–47% of all status epilepticus (SE) cases in the intensive care unit.[25,26] The prevalence of NCS in patients presenting with altered mental status ranged from 8% to 30%.[27] However, all of these data come from small cohort studies, and large population-based studies of the incidence and prevalence of NCS and NCSE remain scarce. The etiology of NCS/NCSE can be classified as follows: underlying epilepsy, acute brain injury, acute systematic insults, and drugs.[7,24]

Among the chronic conditions, epilepsy is most commonly associated with NCSE.[7] It is necessary for clinicians to be vigilant about the possibility that NCSE may be triggered by changes in ASDs or interactions with concomitant medication that lower serum levels of ASDs.[28] About 30%–50% of critical ill patients develop NCSE as a result of the transformation of Generalized convulsive status epilepticus (GCSE) to NCSE.[25,26] This condition is more common in patients with inadequately treated GCSE who eventually transform into subtle SE.

Severe acute brain injury is the most common leading cause of NCSE in the neuro-ICU. In acute stroke patients with SE, NCS and NCSE are more common than convulsive seizures. NCSE occurs in about 15% of comatose ischaemic stroke patients, 18% of patients

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with intracerebral haemorrhage, and 20% of patients with subarachnoid hemorrhage.[2,29–33] 10% of traumatic brain injury patients have NCSE, and 30% of them occur within 3 days after injury.[2,29–33] Leng et al.[34] showed that 57% of critical patients with encephalitis developed NCSE during the course of their illness. In recent years, autoimmune encephalitis has been considered as the most common cause of new-onset refractory SE.[35] The incidence of NCSE in autoimmune encephalitis, especially in different types of autoimmune encephalitis, needs to be clarified. NCSE after hypoxic-ischaemic brain injury usually differs from other acute forms of NCSE, as the underlying brain damage is irreversible and leads to an extremely poor outcome.[7]

Acute systematic insult is another important cause of NCS/NCSE that cannot be ignored, including alcohol, metabolic derangements, intoxication, and autoimmune disorders like systemic lupus erythematosus.[24] During clinical practice, NCS/NCSE can be observed as an adverse drug reaction. Patients receiving cephalosporins have an increased risk of NCSE. Other drugs related with NCS/NCSE are ifosfamide, methotrexate, ketorolac, baclofen, lithium, opioids, and opioid antagonists.[7]

## 7 | CONTINUOUS EEG AND THE PREDICTION OF SEIZURE RISK

Continuous EEG (cEEG) monitoring has now become the standard practice for seizure detection in the ICU,[36,37] particularly in convulsive status epilepticus (CSE) patients who have failed to return to functional baseline after anti-seizure treatment,[38] and in patients with acute neurological injuries in a comatose state with unexplained and persistent altered consciousness.[36] A multicenter, pragmatic, randomized clinical trial, CERTA trial, showed that cEEG had advantages in detecting ictal and interictal discharges compared to the repeated routine EEG and led to an increased modification in ASDs.[39] However, studies investigating the association between the application of cEEG and clinical outcomes have come to a different conclusion. CERTA trial showed that the application of cEEG did not help reduce the mortality or improve functional outcomes,[39] while Hill et al.[40] performed a larger-scale retrospective study and demonstrated that cEEG was associated with lower odds of in-hospital mortality, although the patients in the cEEG cohort appeared to be more severely ill.

Claassen et al. reviewed 570 consecutive patients who underwent cEEG monitoring and found that seizure activity was detected in 19% of patients, and 92% of seizure cases were non-convulsive.[31] The first seizure was detected within the first hour in 56% of patients, after 12 to 24 h in 88%, and after 24 to 48 h of monitoring in 93%.[31] In comatose patients, 20% had their first seizure after 24 h of cEEG monitoring,[31] suggesting that comatose patients usually required prolonged cEEG monitoring to detect seizures. Therefore, some researchers have suggested that when evaluating the presence of NCS and NCSE, it is reasonable to monitor patients who were not in coma for approximately 24 h and monitor comatose patients for 48 to 72 h.[41] Struck et al. described an algorithm of time-dependent electro-clinical risk stratification for electrographic seizures (TERSE) in critical ill patients on cEEG.[42] It includes two pre-cEEG clinical features (history of seizures and coma) and the identification of EEG risk patterns, such as sporadic epileptiform discharges, lateralized periodic discharge (LPDs), lateralized rhythmic spike-and-wave (LSW), LRDA, brief potentially ictal rhythmic discharges (BIRDs), and bilateral independent periodic discharges (BIPDs).[42] If no epileptiform EEG abnormalities emerge, the risk of seizures on cEEG decreases to <5% by 24 h.[42] If a patient had both a history of seizure and was comatose with an EEG risk factor, then for at least 48 h of cEEG monitoring is reasonable.[42] This time-dependent ESz risk stratification model can identify 95% of patients with ESz, while at the same time reducing the duration of required cEEG by two-thirds.[43] In 2017, based on a prospective multicenter database, the 2HELPS2B score (Table 2) was created to estimate the seizure risk in acutely hospitalized patients receiving cEEG.[44] According to the 2HELPS2B score calculated from the first hour of cEEG results, patients can be stratified into 3 categories: low- (2HELPS2B = 0), medium- (2HELPS2B = 1), and high-risk (2HELPS2B ≥2) risk. Each category has an associated minimum recommended duration of cEEG monitoring to avoid missed seizures with a certainty of 95% and 98% (Table 3).[45]

**TABLE 2** 2HELPS2B score

| Risk factors | Score |
|---|---|
| Frequency >2 Hz[a] | 1 |
| Independent sporadic epileptiform discharges | 1 |
| LPD/BIPD/LRDA | 1 |
| Plus features (superimposed rhythmic, fast, sharp)[b] | 1 |
| Prior seizure[c] | 1 |
| BIRD | 2 |

*Note*: Adapted from Aaron F. Struck. JAMA Neurol. 2020;77(4):500–507.[45] & JAMA Neurol. 2017;74(12):1419–1424.[44]

Abbreviations: BIPD, bilateral independent periodic discharges; BIRD, brief potentially ictal rhythmic discharge; LPD, lateralized periodic discharge; LRDA, lateralized rhythmic delta activity.

[a]Frequency of any periodic or rhythmic pattern of more than 2 Hz except GRDA.

[b]Plus features include superimposed rhythmic, fast, or sharp activity only on LRDA, LPDs, or BIPDs.

[c]Prior seizure includes a remote history of epilepsy or recent events suspicious for clinical seizures.

## 8 | TREATMENT

Since sufficient clinical trials on the treatment of NCS and NCSE are still lacking, the optimal treatment protocol of NCS and NCSE has not been established.[7,46] Rapid termination of epileptic activity is the main goal of treatment for NCS/NCSE patients in the neuro-ICU. First of all, treatment needs to be directed towards the underlying etiology. For example, immunomodulation therapies,

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TABLE 3 Seizure risk based on 1-h screening EEG

| Seizre risk group | Recommend duration of EEG monitoring | |
|---|---|---|
| | For seizure risk <5% (h) | For seizure risk <2% (h) |
| Low: 2HELPS2B = 0 | 1 | 3.3 |
| Medium: 2HELPS2B = 1 | 12 | 29 |
| High: 2HELPS2B ≥ 2 | ≥24 | ≥30 |

*Note*: Excludes cardiac arrest patients.

Information obtained from Aaron F. Struck. JAMA Neurol. 2020;77(4):500–507.[45] & Pablo Bravo. Drugs (2021) 81:749–770.[1]

Abbreviation: EEG, Electroencephalogram.

such as corticosteroids and other immunosuppressive measures, are required for patients suspected of having an autoimmune disease. Besides the etiological treatment, the treatments of NCS/NCSE also include the general management and administration of ASDs, which are the scope of this review.

## 8.1 | First-line treatment

Benzodiazepines are usually used as the first-line treatment for NCS and NCSE.[7] Given the demonstrated efficacy, safety, and tolerability, intravenous diazepam, intravenous lorazepam and intramuscular midazolam are recommended as the initial therapy of choice. A 5-year randomized, double-blind, multicenter trial compared the efficacy of four intravenous regimens [diazepam (0.15 mg/kg) followed by phenytoin (18 mg/kg), lorazepam (0.1 mg/kg), phenobarbital (15 mg/kg) or phenytoin (18 mg/kg)] in the treatment of subtle SE.[47] Subtle SE was defined as the patient with coma and ictal discharges on the EEG with or without subtle convulsive movements. No statistically significant differences among the treatments were detected, and the response rate varied from 7.7% to 24.2%.[47]

## 8.2 | Second-line treatment

For those patients who are unresponsive to benzodiazepine therapy, attempts have been made to find a solution. A randomized, blinded, adaptive trial, the Established Status Epilepticus Treatment Trial (ESETT), compared the efficacy and safety of three intravenous anticonvulsive agents – levetiracetam (60 mg/kg, maximum 4500), phenytoin (20 mg/kg, maximum 1500) and valproate (40 mg/kg, maximum 3000) in patients with CSE.[48] Although NCS and NCSE were not specifically included in this trial, patients who had evolved to more subtle signs including nystagmoid or rhythmic eye movements were included, and these ASDs have been widely used to treat NCS and NCSE. This clinical trial has showed that levetiracetam, phenytoin, and valproate each led to seizure cessation and improved alertness by 60 min in approximately half of the patients with similar incidences of adverse events.[48] The Treatment of Recurrent Electrographic Nonconvulsive Seizures trial is the first and only prospective, randomized trial comparing the effectiveness of ASDs in the treatment of NCSs. Using cEEG results as the primary endpoint, the trial found that intravenous lacosamide (LCM), one of the new-generation ASDs, was noninferior to fosphenytoin (fPHT) in controlling NCSs in critically ill subjects, suggesting that LCM is a reasonable treatment alternative for the control of NCSs detected on cEEG in critically ill patients.[49] Besides the abovementioned randomized clinical trials, additional findings on the therapeutic effect of ASDs in patients with NCS and NCSE patients were shaped by the subgroup analyses from larger studies of SE.[1] For perampanel, a retrospective study with a subgroup analysis of NCS/NCSE showed an overall responsive rate of 36% [po (2–10 mg/day)][50] and no difference between the high-dose [po (16–32 mg/day)] and low-dose [po (2–12 mg/day)] groups.[51] In a cohort study on the treatment of refractory and super-refractory SE, 17% of the included patients had NCS/NCSE. The rate of SE cessation attributed to oral topiramate treatment was 27.4%, with a median initial dose 100 mg/day and a median maintenance dose of 400 mg/day.[52] The ASDs commonly used for NCSs and NCSE are summarized in the Table S1.

## 8.3 | Third-line treatment

Since some NCSE patients are refractory to the first- and second-line ASDs described above, especially the NCSE patients with coma, continuous infusion of anaesthetics – midazolam, propofol and high-dose phenobarbitone may be needed. However, previous studies showed that patients treated with intravenous anaesthetic drugs had higher rates of infections and an increased risk of death,[53] and therapeutic coma was associated with poorer outcome at hospital discharge.[54] To date, the appropriate level of aggressiveness of treatment for NCSE is still debated.[55] No consensus has been reached about the depth of coma induction for seizure control purposes.[7]

In the neuro-ICU, the two most common forms of NCSE that clinicians deal with are subtle SE, and NCSE after acute severe brain injury.[1] For patients with the continuation of GCSE in its later, subtle SE requires the same treatment.[55] Aggressive treatments, such as intravenous anesthetic drugs, are preferred when the early ASDs fail.[1,55] When administering anesthetic drugs, clinicians must be aware of the complications arising from anaesthetic drugs, such as the cardiotoxicity from phenobarbitone and the propofol infusion syndrome. Close EEG monitoring is required to make sure the anaesthetic drugs can be reduced as early as possible when NCSE is terminated.[7] For NCSE patients with acute severe brain injury, it is recommended that aggressive medications should be given with caution. In addition to the forms of NCSE, some researchers have also suggested to determine the aggressiveness of treatment by whether the patients are in coma. It is recommended to give comatose patients first- and second-line ASDs with full intravenous loads, and then make a rapid assessment of response. If these ASDs fail to control seizures and there is no improvement in consciousness,

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anesthetic drugs can be attempted.[1] Since NCSE patients without coma usually do not have a poor prognosis compared to NCSE patients with coma, anaesthetic level of medications should be avoided to give to these patients whenever possible.[7]

Seizure burden, expressed as an approximate percentage per epoch, is an important index, based on which clinicians could modify the treatment for NCS and NCSE patients accordingly. Payne et al. found that a seizure burden exceeding 20% in a given hour was strongly associated with neurological decline.[4,56] It has been suggested to take seizure burden into consideration when planning aggressiveness of treatment, especially in scenarios in which seizure freedom is not achievable, either from lack of treatment efficacy or risk of additional aggressive treatment. However, it is still unknown what the exact rate of reduction of seizure burden is considered acceptable.[1] Prognostic clinical scores are another reference tool when clinicians are unsure whether the risks associated with aggressive therapy are balanced with the potential benefits of improved outcomes. Status Epilepticus Severity Score (STESS) is a clinical score for the prognosis of SE in adults and a tool to orient early treatment strategies.[57,58] Most patients with low scores will almost certainly survive their SE episode and may return to clinical baseline, so immediate aggressive treatment might possibly be avoided for these patients.[57] Epidemiology-Based Mortality Score in Status Epilepticus (EMSE), which uses a combination of epidemiology-derived data including aetiology, age, comorbidity and EEG, is another important clinical score for predicting SE outcomes.[59] It is also a valuable tool for risk stratification, and sometimes it yields significantly better results than STESS.[59] All cases of NCS and NCSE should be treated vigorously and receive close clinical follow-up. Clinicians are suggested to consider the etiologies, types of NCS/NCSE, EEG patterns, side effects of medications, age, social (family) setting, medical comorbidities, and overall prognosis when developing the treatment strategies.[55] Figure 3 shows the suggested stepwise approach for the treatment of NCS and NCSE.

## 9 | PROGNOSIS

Patients with NCSE/NCS often have both prolonged ICU and hospital stay.[26] However, till now, the prognostic values of clinical characteristics and EEG findings have not been fully assessed in the specific context of NCS/NCSE. Usually, critically ill patients with NCSE have a worse outcome than non-critically ill patients with NCSE. A previous study showed that approximately 50% of NCSE/NCS survivors were discharged with new neurological deficits and 25% returned to baseline neurological status.[26] The mortality rates in elderly patients range from 15% to 52%.[60] The outcomes of NCS/NCSE are driven largely by the etiology,[7] apart from coexisting medical or critical illnesses.[23] In patients with acute severe brain injury, it is difficult to distinguish between brain damage causing NCSE and damage caused by seizures,[61] but early diagnosis and treatment of ictal activity can reduce morbidity in these patients. Remarkably, NCS should not be

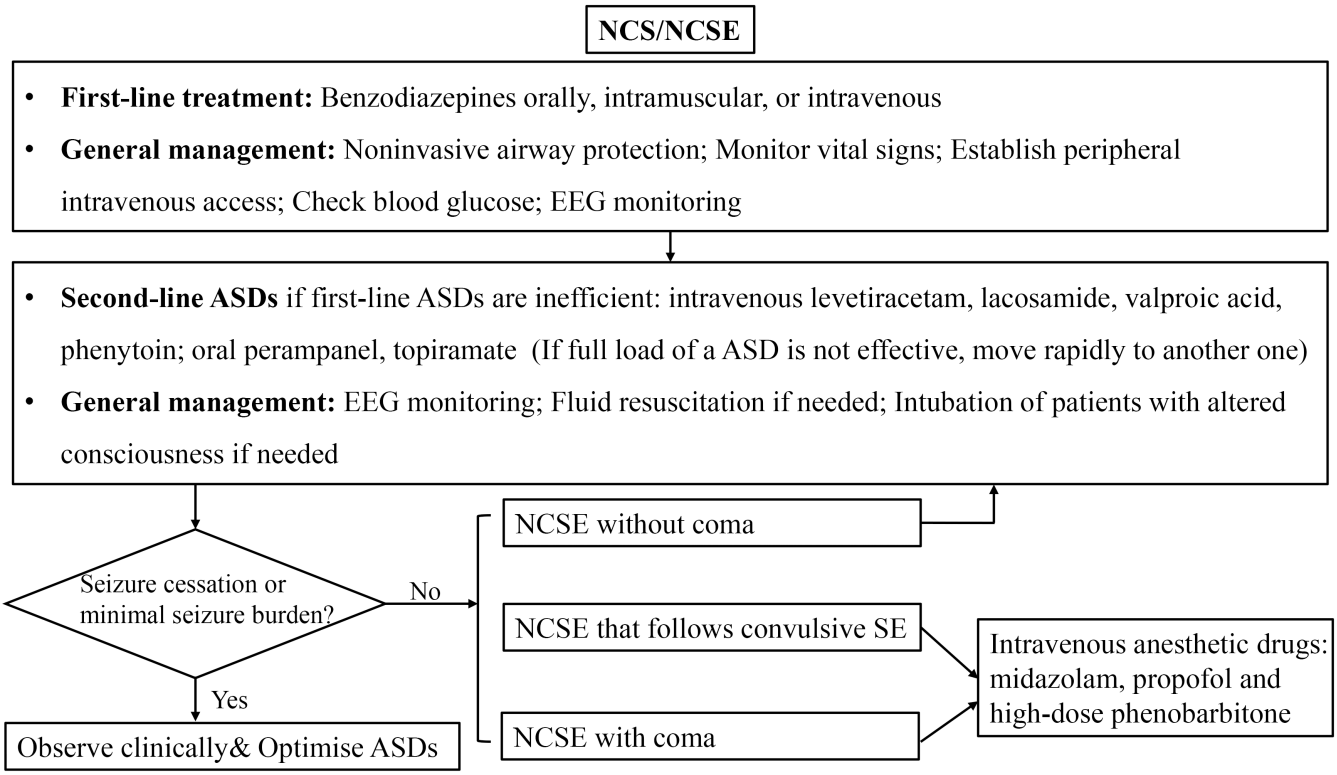
NCS/NCSE
First-line treatment: Benzodiazepines orally, intramuscular, or intravenous
General management: Noninvasive airway protection; Monitor vital signs; Establish peripheral intravenous access; Check blood glucose; EEG monitoring
Second-line ASDs if first-line ASDs are inefficient: intravenous levetiracetam, lacosamide, valproic acid, phenytoin; oral perampanel, topiramate (If full load of a ASD is not effective, move rapidly to another one)
General management: EEG monitoring; Fluid resuscitation if needed; Intubation of patients with altered consciousness if needed
Seizure cessation or minimal seizure burden?
No
Yes
Observe clinically& Optimise ASDs
NCSE without coma
NCSE that follows convulsive SE
NCSE with coma
Intravenous anesthetic drugs: midazolam, propofol and high-dose phenobarbitone

FIGURE 3 Suggested stepwise approach for treatment of NCS and NCSE. NCS, non-convulsive seizure; NCSE, non-convulsive status epilepticus; EEG, electroencephalogram; ASDs: anti-seizure drugs. Information obtained from Raoul Sutter. Nat Rev Neurol 2016. 12(5):281–293[7] & Pablo Bravo. Drugs. 2021. 81:749–770[1]

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considered as a poor prognostic factor in critical ill encephalopathic cancer patient, in contrast to other populations.[62] The prognosis of NCSE patients also depends on a detailed assessment of the type of NCSE and the level of consciousness.[63] Sometimes, EEG findings may also provide prognostic values to some extent. A prospective observational study on NCS/NCSE in the neuro-ICU showed that subjects with generalized ictal discharges had a worse prognosis compared to those with unilateral ictal discharges.[26] Serum neuron-specific enolase (NSE), a marker of neuronal injury, increases after NCSE, but its prognostic value in SE is unclear.[7]

## 10 | CONCLUSIONS

NCS and NCSE are common in the neuro-ICU, especially following GTCS and acute brain injury. The various subtle clinical symptoms of NCS/NCSE make the diagnosis challenging, but the application of cEEG has helped improve the diagnosis in recent years. The Salzburg Consensus Criteria delineate four EEG patterns of NCSE and have become the most widely used and important diagnostic basis for NCSE. The treatments of NCS/NCSE are often individualized and need to target on the underlying etiologies. Standardized protocols for the management of NCS and NCSE are urgently needed. Future research will be required to determine the association between characteristic EEG patterns and clinical outcomes, and whether ASDs are necessary for patients with possible NCSE and improve their prognosis.

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### CONFLICT OF INTEREST

There are no conflicts of interest.

### PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/ane.13718.

### DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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